UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

June 25, 1999

MEMORANDUM

SUBJECT: ***COUMAPHOS: RE-EVALUATION of Toxicology Endpoints Selection for Dermal Risk Assessments*** **- Report of the Hazard Identification AssessmentReview Committee (HIARC)**

FROM: Nicole Paquette, Ph.D.
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THROUGH: Pauline Wagner, Co-Chair
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Health Effects Division (7509C)
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TO: Christina Jarvis
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PC Code: 036501

On June 24, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated a 2 and 5-day dermal toxicity study in rats (MRID 44749401) and re-evaluated the 21-day dermal toxicity study dose previously selected for the short term exposure risk assessment. The HIARC concluded that the dermal NOAEL from the 5 day dermal study should be used for short term dermal exposure scenarios for Coumaphos. **THIS DOCUMENT SUPERSEDES THE PREVIOUS HIARC DOCUMENT DATED JANUARY 5, 1995.**

Committee Members in Attendance

Members present: William Burnam, Karen Hamernik, Pam Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, Kathleen Raffaele,David Anderson, Virginia Dobozy, Pauline Wagner, Jess Rowland, PV Shah and Brenda Tarplee (Executive Secretary).

Data was presented by Nicole Paquette of Reregistration Branch 2.

Data Presentation and Report Preparation: Nicole C. Paquette, Ph.D.
Toxicologist

Report Concurrence: _____
Brenda Tarplee
Executive Secretary

I. INTRODUCTION

On **January 5, 1995** the Health Effects Division's Toxicology Endpoint Selection Committee (TES) evaluated the toxicology database for coumaphos and selected doses and endpoints for acute and chronic dietary as well as occupational exposure risk assessments.

On **September 8, 1997**, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Coumaphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Coumaphos as required by the Food Quality Protecting Act (FQPA) of 1996. (HIARC Report dated September 25, 1997) The FQPA requirement was not addressed in the Reregistration Eligibility Document.

During **May 12 through 14, 1998**, the HIARC conducted a comprehensive review of 40 organophosphates including, coumaphos. At this meeting, following a consistency review of the doses and endpoints selected for dietary and non-dietary exposures. On **June 15 and 16, 1998**, the FQPA Safety Factor Committee (FQPA SFC) evaluated hazard and exposure data for coumaphos and determined that the 10 x to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 3 x because of data gap for acute and subchronic neurotoxicity studies (Combined HIARC/FQPA Report dated August 6, 1998).

On **May 11, 1999** the Hazard Identification Assessment Review Committee (HIARC) met to evaluate the impact that the results of recently submitted acute (MRID No. 444544801) and subchronic (MRID: 44775901) neurotoxicity studies in the rat would have on risk assessment endpoints. The HIARC determined that the acute neurotoxicity study was a more appropriate since the endpoint (cholinesterase inhibition) was seen following a single oral (gavage) dose and thus suitable for this (acute) risk assessment, rather than the previous endpoint (cholinesterase inhibition) measured at 21 day time point in the 13-week dietary study in rats (MRID 00126527). On **May 17, 1999** the FQPA Safety Factor Committee met to reevaluate the hazard and exposure data for coumaphos, and, recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed (1x) because the data gap for the two neurotoxicity studies was fulfilled, The FQPA safety factor recommendation in this report supercedes that previously reported for coumaphos in the *FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES* dated August 6, 1998.

On **June 24, 1999**, HIARC reviewed a recently submitted shorter term dermal toxicity study (2 and 5 day dermal exposure) and evaluated its appropriateness for use in a short term dermal exposure risk assessment. Previously, the HIARC selected a 21-day dermal toxicity study in rats (MRID 42666401) for use a short term dermal risk assessment. (HED Doc. 013140).

II. HAZARD IDENTIFICATION

A. Acute Dietary (one day)

Study Selected: Acute Neurotoxicity Study in Rats

Executive Summary: In an acute oral neurotoxicity study (MRID 44544801), 18 Wistar rats/gender/exposure group were administered single doses of Coumaphos (purity, 95.2%) at 0, 2, 75, or 250 mg/kg (males) or doses of 0, 2, 10, or 17.5 mg/kg (females) by gavage. It should be noted that the doses in male rats were 7 to 14 times greater than the doses administered to females. In a range finding study, the lowest lethal dose for male rats was 350 mg/kg; the lowest lethal dose in females was 20 mg/kg.

All animals survived to scheduled termination. Clinical symptoms were observed in both males and females, primarily in the high-dose groups, and included marked cholinergic signs including piloerection, decreased motility, abnormal gait, extension spasms, tremors, breathing abnormalities, coolness to touch, oral stains, and decreased reactivity. Clinical symptoms began on the day of treatment and continued through day 12 for males (piloerection) and day 3 for females (piloerection, decreased motility, gait abnormalities, and decreased reactivity). Body weights were statistically significantly depressed on days 7 and 14, respectively, only in male rats in the high dose group. The following FOB parameters were statistically significantly different from controls in high dose males (250 mg/kg) only on the day of treatment: gait, clonic movements, decreased activity, salivation, oral stains, respiratory abnormalities, rearing, and forelimb and hindlimb grip strengths. With the exception of one male with uncoordinated and stilted gait, all of these effects were reversed after day 8. The following FOB parameters were statistically significantly different from controls in high-dose females (17.5 mg/kg) on the day of treatment: clonic movements and forelimb grip strength, both reversed by day 7. Motor activity and locomotor activity were depressed for males in the high-dose group, but these changes were not statistically significant. Erythrocyte (RBC) cholinesterase activity in males and plasma and erythrocyte cholinesterase activities in females were significantly depressed in the low-dose (2 mg/kg) groups ($p \leq 0.05$ or $p \leq 0.01$). No treatment-related neuropathological effects were observed.

The critical toxic effect in this study was plasma and RBC cholinesterase inhibition (LOAEL = 2 mg/kg) in both males and females. A NOAEL for cholinesterase inhibition was not established.

Dose and Endpoint for establishing the acute RfD: LOAEL = 2 mg/kg based on plasma and RBC ChE inhibition in male and female rats; no NOAEL was established.

Uncertainty Factor: 300 (10 x for interspecies extrapolation and 10 x for intraspecies variablity and 3 x for lack of a NOAEL.

Acute RfD = $\frac{\text{2.0 mg/kg}}{\text{300 (UF)}}$ **= 0.007 mg/kg**

This risk assessment is required.

B. Chronic Dietary : (from TES HED Doc #No. 013140 (01/02/95)

Study Selected: Chronic toxicity study in the Dog

Executive Summary: In a 1-year feeding study (MRID 43055301) male and female Beagle dogs (4 per sex/group) were given coumaphos(98.0-99.0%) in the diet at concentrations of 0, 1, 30, or 90 ppm (equivalent to 0.025, 0.775, or 2.295 mg/kg/day for males, and 0.024, 0.705, or 2.478 mg/kg/day for females, respectively). Control groups received untreated diet.

When compared to pretreatment values, plasma cholinesterase (ChE) and erythrocyte cholinesterase (RBC ChE) activity levels were significantly depressed ($p \leq 0.05$) in the 30 and 90 ppm exposure groups. Specifically, plasma ChE levels in 30 ppm males at 91, 182, 273, and 363 days were 62.5%, 73.6%, 72.1%, and 76.1% less than pretreatment values and in 30 ppm females were 53.8%, 62.0%, 61.7%, and 72.1% less than pretreatment levels. In the 90 ppm groups, plasma ChE activity at days 91, 82, 273, and 363 were depressed 70.8%, 73.8%, 80.2% and 77.9% (males) and 74.4%, 76.5%, 73.4%, and 84.4% (females). For RBC ChE activity levels in the 30-ppm group at these time points, the respective values were 41.9%, 37.3%, 42.4%, and 46.6% (males), and 49.3%, 33.9%, 42.1% and 42.9% (females) of respective pretreatment values. RBC ChE activity levels in the 90 ppm group at days 91, 182, 273, and 363, were 76.9%, 66.2%, 75.2%, and 59.7% (males), and 79.2%, 75.1%, 82.1% and 75.6% (females) less than the pretreatment values. Comparison to concurrent controls and evaluation of brain cholinesterase and ocular muscle cholinesterase at the termination of the study corroborated these findings. Although some statistically significant depression of PChE was also observed in females in the 1 ppm group, the difference could be attributed to the high degree of individual variability. **Based upon significant and biologically relevant depression of RBC ChE and plasma ChE activity levels in dogs, this study provided a NOAEL = .025 mg/kg/day and a LOAEL = 0.77 mg/kg/day.**

There were no other treatment related systemic changes at any dose level. The systemic NOAEL was 2.3 mg/kg/day and the LOAEL was greater than 2.3 mg/kg/day.

Dose and Endpoint for Establishing the RfD: NOAEL = 0.025 mg/kg based on RBC and plasma ChE inhibition in male and female dogs at 0.77 mg/kg.

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability.

Chronic RfD - $\frac{\text{0.025 mg/kg}}{\text{100 (UF)}}$ **= 0.0003 mg/kg**

This risk assessment is required.

C. Occupational Exposure

1. Dermal Absorption (from TES HED Doc #No. 013140 (01/02/95)

In the absence of dermal absorption data and considering the observation that erythrocyte cholinesterase inhibition is observed in both gavage and dermal rat studies at similar dose levels, the default of 100 % absorption should be used**.**

% absorbed: The dermal absorption should be considered to be 100 %.

2. Short-Term Dermal Exposure (1-7 days)

Study Selected: 2 & 5 Day Dermal Toxicity Study in Female Rats

Executive Summary: In a repeated 2 and 5 day dermal toxicity study (MRID 44749401), Sprague Dawley female rats (6 rats/dose) were treated dermally with coumaphos (95.2% purity) as neat material moistened with deionized water at doses of 0, 2.5, 5, 10, 20, and 50 mg/kg/day for 6 hours/day. Sites were covered with an occlusive bandage. Only female rats were used since females were consistency more sensitive to the cholinergic and lethal effects than males .

No mortality was observed and there were no biological significant treatment related effects on body weight, brain weight or cholinergic signs in either the 2 day or the 5 day exposure period. Nasal discharge and lacrimation were noted in control and treated animals and were attributed to the use of collars. Organ weights, clinical chemistries, hematological and histological examinations (other than brain histology) were not conducted since the previous 21 day dermal study (MRID 44666401) established that the NOAEL for any effect on these parameters was 100 mg/kg.

2-Day Dermal

Brain cholinesterase (ChE) activity was statistically significantly inhibited (11%) in animals treated with 50 mg/kg. Plasma and red blood cell (RBC) cholinesterase activity were slightly reduced at 50 mg/kg but were not statistically significant. Plasma ChE activity was reduced by 19% or 26% compared to concurrent control or pretreatment values, respectively. Red blood cell ChE was inhibited by 23 % or 21 % compared to concurrent control group or pretreatment values, respectively. **Based on cholinesterase inhibition in the brain, plasma and RBC at the highest dose (LOAEL = 50 mg/kg), the NOAEL was 20 mg/kg.**

5-Day Dermal

Plasma, RBC and brain cholinesterase activity was significantly reduced by 25%, 30% and 15%,

respectively, in the 50 mg/kg dose group at termination. RBC (29%) and brain(10%) cholinesterase were statistically significantly inhibited in the 20 mg/kg dose group. Brain cholinesterase was also inhibited by 12% in the 10 mg/kg group. **The NOAEL was 5 mg/kg based on brain cholinesterase inhibition in female rats at 10 mg/kg (LOAEL).**

Dose and Endpoint Selected: NOAEL = 5 mg/kg, based on brain ChE inhibition in female rats at 10 mg/kg from the 5-Day repeated dermal toxicity study.

Comments about Study/Endpoint: **This dose and endpoint replaces the previous short term dermal endpoint from the 21 day dermal toxicity study (MRID 42666401).** Based on some of the use-patterns and potential exposure scenarios for coumaphos, workers will be exposed to coumaphos for less than 21 days and a shorter term exposure dermal toxicity study is more appropriate to assess worker risk. The toxicity endpoint from the 5 day dermal toxicity study (NOAEL=5.0 mg/kg) should be used for risk assessment purposes instead of the toxicity endpoint (NOAEL = 20 mg/kg) from the 2 day dermal because the study better characterizes the shape of the dose response for the critical effect (plasma, RBC, brain ChE inhibition). There is high level of confidence in the NOAEL from the 5-day dermal study and should be used. In addition, the toxicity endpoint (NOAEL) from the 2 day study will underestimate the worker risk because short term exposure is defined as exposure to a pesticide from one to seven days.

Comment on Dose/Endpoint: For occupational short term dermal exposure risk assessments , a NOAEL = 5.0 mg/kg should be used based on brain cholinesterase inhibition in female rats at 10 mg/kg from a 5-day dermal toxicity study. This toxicity endpoint would replace the short term dermal exposure NOAEL (0.5 mg/kg) from a 21-day dermal toxicity study in rats based on RBC ChE inhibition in female rats at 1.1 mg/kg.

This risk assessment is required.

3. Intermediate Term Dermal Exposure (from TES HED Doc #No. 013140 (01/02/95)

Study Selected : 21-day dermal study in the rat (83-2); two studies

MRID: 1) 42084901, 2) 42666401

Executive Summary: In a 21-day dermal study coumaphos was administered to 6 male and female Sprague-Dawley [Sas:CD(SD)BR] rats per group at doses of 0, 2, 4, 20 or 100 mg/kg/day for 21 days.

> At 2 mg/kg/day (LDT) there was erythrocyte cholinesterase (RBC ChE) inhibition in males (20, 24, 84 and 96 % from low to high dose) and females (14, 42, 89 and 95 % from low to high dose) and plasma ChE inhibition in females (38, 38, 65 and 91 % from low to high dose). At 20 and 200 mg/kg/day plasma (males - 44, 78 % for the 2 high doses) and brain ChE were decreased in males (22 and 59 % for 2 highest doses) and females (26 and 67 % for 2 highest doses). **The LOAEL for cholinesterase inhibition is**

equal to or less than 2 mg/kg/day based on RBC and plasma ChE). The NOAEL for cholinesterase inhibition is less than 2 mg/kg/day.

Signs of systemic toxicity occurred at 20 mg/kg/day and above and included muscle fasciculation in males (17 and 67 % for 2 high doses) and females (17 and 100 % for 2 high doses) sporadically throughout the study. Tremors occurred in females (17 and 83 %) after the first week and there were anal stains in males. At 100 mg/kg/day there was increased incidence of hypothermia and activity in females and decreased body weight gains in males and females. The systemic LOAEL is 20 mg/kg/day based on muscle fasciculation and tremors. The systemic NOAEL is 4 mg/kg/day.

This study is classified as core-supplementary data (a NOEL for ChE was not determined) when considered alone and is not acceptable for regulatory purposes. However, the study is considered core-minimum when taken together with a second study conducted using lower doses in females (MRID 42666401).

2) In a 21-day dermal study coumaphos4(MRID 42084901) was administered to 5 female Sprague-Dawley [Sas:CD(SD)BR] rats per group at doses of 0, 0.1, 0.5, 1.1 or 2.1 mg/kg/day for 21 days.

At 1.1 mg/kg/day RBC ChE was inhibited (24 and 28 % for 2 high doses). **The LOAEL for cholinesterase inhibition is 1.1 mg/kg/day based on RBC ChE in females. The NOAEL for cholinesterase inhibition is 0.5 mg/kg/day.**

There was no systemic toxicity observed at any dose. The systemic LOAEL is greater than 2.1 mg/kg/day. The systemic NOAEL is 2.1 mg/kg/day (4 mg/kg/day based on a separate study).

This study (MRID 42084901) is considered core-minimum when taken together with study #1 (MRID 42666401 above.

Dose and Endpoint for use in risk assessment: The endpoint for short term occupational or residential risk assessment is the ChE NOEL (0.5 mg/kg/day) from the 21-day dermal rat study. The LEL (1.1 mg/kg/day) is based upon inhibition of RBC ChE.

This risk assessment is required.

4. Long Term Dermal Exposure

The use pattern and exposure scenarios do not indicate a need for long term dermal risk assessment.

5. Short Term Inhalation Exposure

Study Selected : Acute Neurotoxicity Study in Rats (MRID 44544801)

Executive Summary: See Acute Dietary

Dose and Endpoint for establishing the acute RfD: LOAEL = 2 mg/kg based on plasma and RBC ChE inhibition in male and female rats; no NOAEL was established.

A Margin-Of-Exposure (MOE) of 300 is required for short term inhalation occupational risk assessment and includes the conventional 100 and an additional 3x factor for the use of a LOAEL (i.e. lack of a NOAEL in the study).

This risk assessment is required.

6. Intermediate Term Inhalation Exposure (from TES HED Doc #No. 013140 (01/02/95)

Study Selected: 13-week dietary study in the rat (MRID: 00126527)

Executive Summary: In a 13 week study (MRIS 00126527) coumaphos was administered in the diet to 20 Charles River [Crl:CR®(SD)Br] rats per sex per group at doses of 0, 2, 5 or 10 ppm (0, 0.2, 0.5 or 1.0 mg/kg/day) for 13 weeks. Plasma, erythrocyte (RBC) and brain cholinesterase (ChE) were determined at 3, 8 and 13 weeks.

Plasma cholinesterase was inhibitied throughout the study at all doses in males but only statistically significant at 10 ppm (16, 15 and 24*%, from low to high dose) and for males at 10 ppm (not significant, 21%). RBC ChE was significant inhibited in males (18*, 34*, 50%*, from low to high dose) and females (32*, 39*, 64*%, from low to high dose) at all doses and time points wxcept at 2 ppm values where significance occurred only at 13 weeks. Brain ChE was not inhibited at any time. **The LOAEL for cholinesterase inhibition is equal to or less than 2 ppm (0.2 mg/kg/day) base on RBC ChE inhibition. The NOAEL for cholinesterase inhibition is less than 2 ppm.**

There were no signs of systemic toxicity abserved at any dose. The systemica LOAEL and NOAEL are greater than 10 ppm (1.0 mg/kg/day).

This study is classified as core-supplementary, however it can be used for regulatory purposes in setting levels for risk assessment

Dose and endpoint used for intermediate term inhalation risk assessment: LOAEL = 0.2 mg/kg, based on RBC ChE inhibition which occurred at 13 weeks. No NOAEL was established.

A Margin-Of-Exposure (MOE) of 300 is required for short term inhalation occupational risk assessment and includes the conventional 100 (10x for interspecies extrapolation and 10x for

intraspecies variability) and an additional 3x factor for the use of a LOAEL (i.e. lack of a NOAEL in the study).

This risk assessment is required.

7. Long Term Inhalation Exposure

The use pattern and exposure scenarios do not indicate a need for long term inhalation risk assessment.

III. FQPA CONSIDERATIONS

II 1. Neurotoxicity

- **#** In an acute delayed neurotoxicity study, no delayed neurotoxicity was seen in hens given a single oral dose (via gelatin capsule) of Coumaphos at 50 mg/kg (MRID No. 00115167). The Committee noted that this study did not assess for the potential of Coumaphos to inhibit neurotoxic esterase (NTE) in hens.

- **#** No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, behavioral effects and histopathology of the central and peripheral nervous systems are not available.

2. Developmental Toxicity

- **#** The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to Coumaphos and comparable NOELs were established for adults and offspring.

- **#** In a developmental toxicity study pregnant Crl:COBS-CD(SD) rats received oral doses of Coumaphos at 0, 1, 5 or 25 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 5 mg/kg/day and the LOEL was 25 mg/kg/day based on clinical signs of cholinesterase inhibition. For developmental toxicity, the NOEL was 25 mg/kg/day (HDT); a LOEL was not established. There was no evidence of teratogenicity (MRID No. 00131684).

- **#** In a developmental toxicity study, pregnant American Dutch rabbits were given single oral dose of Coumaphos at 0, 0.25, 2, or 18 mg/kg/day during gestation days 7 through 19. For maternal toxicity, the NOEL was 2 mg/kg/day and the LOEL was 18 mg/kg/day based on mortality (2/17) and cholinergic signs. For developmental toxicity, the NOEL was 18 mg/kg/day (HDT); a LOEL was not established. There was no evidence of teratogenicity (MRID No. 00131683).

3. Reproductive Toxicity

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Coumaphos at 0, 1, 5 or 25 ppm (0, 0.07, 0.3, or 1.79 mg/kg/day in males and 0, 0.08, 0.34 or 2.02 mg/kg/day in females, respectively). There was no increased sensitivity to pups over the adults. For parental/systemic toxicity, the NOEL was 25 ppm (1.79 mg/kg/day, (HDT); a LOEL was not established. For reproductive toxicity, the NOEL was 25 ppm (1.79 mg/kg/day); a LOEL was not established (MRID No. 430611701).

4. Cholinesterase Inhibition

Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies. In the reproduction study, ChE activity was measured in adults and pups. There was dose-related decreases in plasma and red blood cell cholinesterase activity in dams at 5 and 25 ppm. Generally, no differences were seen on day 47 and day 91 measurements. Brain levels were biologically significantly inhibited (30%) in F_o and F_1 adult females at 25 ppm, and in F_o adult males at 25 ppm. In pups, no significant changes in red blood cell or brain cholinesterase activity were seen on day 4, but on day 21 changes were seen at 25 ppm. In F_1 pups, plasma and red blood cell ChE inhibition of 38-44% was seen, while in F_2 pups, only plasma was affected (31-44%). The only significant brain inhibition in pups was an 8% decrease in F_1 females on day 21. The NOEL was 5 ppm for cholinesterase inhibition in dams and in pups on day 21 (MRID No. 430611701).

5. Determination of Susceptibility

Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to coumaphos. There was no indication of increased susceptibility in the offspring as compared to parental animals in the 2-generation reproduction study. In these studies, effects in the fetuses/offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

6. Determination of Need For Developmental Neurotoxicity Study

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to coumaphos. These include acceptable developmental toxicity studies in rats and rabbits, as well as, a 2-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen after acute and subchronic exposure to rats. Additionally, there was no evidence of abnormalities to the fetus to the fetal nervous system in the pre- and post-natal studies. Based on the weight-

of-evidence, the HIARC determined that a developmental neurotoxicity study in rats is not required for coumaphos.

7. **Determination of the FQPA Safety Factor**

Previously for coumaphos, the FQPA safety factor recommendation was 3x due to the data gaps for the acute and subchronic neurotoxicity studies (*FQPA Safety Factor Recommendations for the Organophosphates* dated August 6, 1998). Now that these data requirements have been satisfied, the Committee recommended that the FQPA safety factor be removed (1x). (FQPA Report dated June 1, 1999)

SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Toxicological enpoints for risk assessments with coumaphos are tabulated below:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	LOAEL= 2.0 UF = 300	Plasma ChE inhibition in females and RBC ChE Inhibition in both male and female rats	Acute Oral Neurotoxicity in Rats	Not Relevant
	Acute RfD = 0.007 mg/kg/day			
Chronic Dietary	NOAEL=0.025 UF = 100	Plasma and RBC ChE Inhibition in both male and female dogs	Chronic Toxicity -Dog	Not Relevant
		Chronic RfD = 0.0003 mg/kg/day		
Short-Term (Dermal)	NOAEL=5.0	Brain ChE Inhibition in female rats	5-Day Dermal Study in Female Rats	100
Intermediate-Term * (Dermal)	NOAEL=0.5	RBC ChE Inhibition in female rats	21-Day Dermal Study in Rats	100
Long-Term (Dermal)	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment		----
Short-Term * (Inhalation)	Oral LOAEL= 2.0	Plasma ChE Inhibition in females and RBC ChE Inhibition in males and female rats	Acute Neurotoxicity Study in Rats	300

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Intermediate-Term * (Inhalation)	Oral LOAEL = 0.2	RBC ChE Inhibition in rats	13-Week Dietary Study in Rats	300
Long Term (Inhalation)[1]	None	The use pattern and exposure scenario do not indicate a need for long term risk assessment		**---**

1 Oral values were selected therefore route-to-route extrapolation must be used (assume 100% inhalation absorption).

***** MOE for worker exposure risk assessments = 100; no residential uses registered

Acute Toxicity Endpoints

The table below summarizes the results of acute toxicity studies on coumaphos:

TEST	RESULT	CATEGORY
Oral LD50 in rat (MRID 00110597)	>240 mg/kg - males 17 mg/kg - females	I
Dermal LD50 in rat (MRID 00110598)	> 2400 mg/kg - males and females	III
1 hour Inhal. LC50 in rat (MRID 00110601)	1.081 mg/l - males 0.341 mg/l - females	II
Eye irrit. in rabbit (MRID 00110599)	Mild irritant, resolved by day 7	III
Dermal irritation in rabbit (MRID 00110600)	Not irritating	IV
Dermal sensitization in Guinea pig (MRID 00110602)	Not a sensitizer	N/A
Acute neurotoxicity in hen	Does not produce delayed toxicity	N/A

Hazard Characterization

Coumaphos is highly acutely toxic via the oral route and moderately toxic by dermal, and inhalation routes. Toxic symptoms are largely caused by the inhibition of cholinesterase. In the

acute oral toxicity studies, female rats are approximately 17 times more sensitive to the toxic and lethal effects of coumaphos compared to male rats. In a single dose oral study, females rats had cholinesterase inhibition and cholinergic symptoms at much lower doses than male rats. In a short term (5 days) dermal toxicity study brain cholinesterase inhibition was the most sensitive indication of the toxic effects of coumaphos dermal treatment. Coumaphos is not a dermal sensitizer or a dermal irritant and does not cause delayed neuropathy. Dermal absorption is estimated to be 100%. This estimate is based on the observation that erythrocyte cholinesterase inhibition is observed in both oral and dermal rat studies at similar dose levels.

Coumaphos primarily affects the nervous system through cholinesterase inhibition. following exposure for various durations. In general, females are consistently more sensitive to the cholinergic effects than males. In subchronic and chronic studies in rats, the magnitude of cholinesterase inhibition in red blood cell and plasma and brain was more pronounced in females compared to males. In chronic studies, the only systemic effect other than cholinergic toxicity was a decrease in body weight gain in male and female rats.

Coumaphos is not a developmental toxicant and has no effect on reproduction. In developmental toxicity studies in rats and rabbits and a two-generation reproduction study there was no evidence of malformations or decreases in the number of pups and/or litter or surviving offspring.

Coumaphos is not carcinogenic and is classified as a Group E chemical, indicating that it is "Not Likely" to be carcinogenic in humans via relevant routes of exposure. This classification is based on adequate studies in two animal species. No evidence of mutagenicity was seen in any study.

Following oral administration, coumaphos is rapidly broken down into nontoxic metabolites and eliminated in urine and feces with no evidence of bioaccumulation. The plasma half life ranges from approximately 3 to 5 hours. Tissue residues of coumaphos are highest in fat, kidney, liver and muscle. Approximately 63 - 83% of administered dose is excreted in the urine within 24 hours and 76-96% is excreted within 7 days.

IV. DATA GAPS

None. The toxicology database for coumaphos was complete.